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Regioselective Palladium-Catalyzed Electrophilic Allylic Substitution in the Presence of Hexamethylditin

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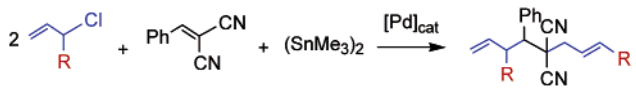
ABSTRACT



Palladium-catalyzed electrophilic allylic substitution of functionalized allyl chlorides and allyl acetates can be achieved in the presence of hexamethylditin under mild reaction conditions. The substitution reaction occurs with very high regioselectivity at the branched allylic terminus. Regioselective tandem bisallylation reaction could be performed by employing benzylidenemalonitrile as substrate. The reaction mechanism can be explained by involvement of a bisallylpalladium intermediate. A particularly interesting mechanistic feature of this reaction is that palladium catalyzes up to three different transformations in the same catalytic cycle. DFT calculations indicate that the regioselectivity is determined by the location of the allylic substituent in the η^1-allyl moiety of the reaction intermediate.

Palladium-catalyzed allylations of electrophilic reagents have recently been the subject of great interest in the synthetic community due to their wide scope, practical simplicity, and potential for regio- and stereoselective synthesis.[1] In many of these reactions organopalladium compounds derived from halides or esters undergo transmetalation with organometallic reagents[2] (such as $SnCl_2$, $ZnEt_2$, Et_3B, etc.) transforming the electrophilic palladium intermediates into nucleophilic organometallic compounds. These organometallic compounds formed as transient intermediates react with an electrophilic partner in situ. Another strategy involves use of allylstannanes and allyl chlorides with catalytic amounts of palladium to form intermediary bisallylpalladium complexes,[3,4] which readily react with electrophiles. Although this reaction has a great synthetic potential, as it can be extended to tandem bisallylation of appropriate substrates,[3b,c,4] it has been mainly employed for the parent or simple methyl-substituted allylic precursors. This synthetic scope can be ascribed to the complex reactivity of the bisallylpalladium intermediates, as well as to the poor availability of properly functionalized allylstannane precursors.

We have now found that the two above strategies can be combined by palladium-catalyzed formation of the transient allylstannanes followed by generation of a bisallylpalladium intermediate, which subsequently reacts with electrophiles.

Thus, when allyl acetates or chlorides were reacted with aldehyde or imine electrophiles, the corresponding homoallyl alcohol or amine product could be obtained in good yield (Scheme 1 and Table 1). When benzylidenemalonitrile was employed with 2 equiv of allylic substrate, a tandem bisallylation reaction could be performed (Scheme 1).

In a typical reaction the corresponding electrophile **6**−**9** (0.3 mmol) and palladium catalyst (5 mol %) was dissolved

(1) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

(2) (a) Tamaru, Y. *J. Organomet. Chem.* **1999**, *576*, 215. (b) Masayuma, Y.; Kinugawa, N.; Kurusu, Y. *J. Org. Chem.* **1987**, *52*, 3702. (c) Shimizu, M.; Kimuro, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1988**, *39*, 609. (d) Masayuma, Y.; Otake, K.; Kurusu, Y. *Tetrahedron Lett.* **1988**, *29*, 3563. (e) Kimura, M.; Kiyama, I.; Tomizawa, T.; Horino, Y. Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1999**, *40*, 6795. (f) Tamaru, Y.; Goto, S.; Tanaka, A.; Shizimu, M.; Kimura, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 878.

(3) (a) Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641. (b) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113. (c) Nakamura, H.; Aoyagi, K.; Shim, J.-G., Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372. (d) Kiji, J.; Okano, T.; Nomura, T.; Saiki, K.; Sai, T.; Tsuji, J. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1939.

(4) (a) Solin, N.; Narayan, S.; Szabó, K. J. *J. Org. Chem.* **2001**, *66*, 1686. (b) Solin, N.; Narayan, S.; Szabó, K. J. *Org. Lett.* **2001**, *3*, 909.

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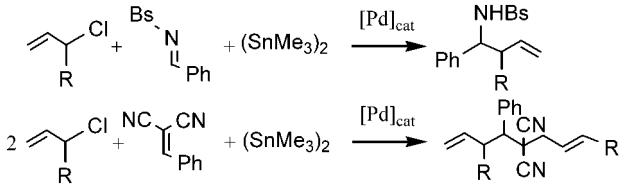
Scheme 1

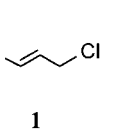
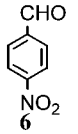
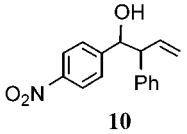
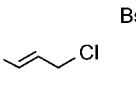
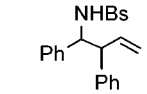
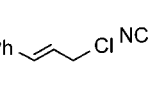
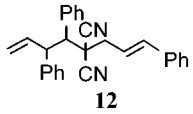
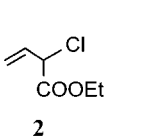
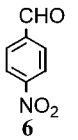
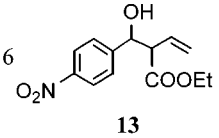
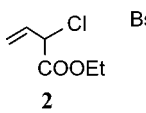
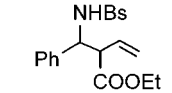
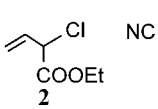
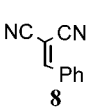
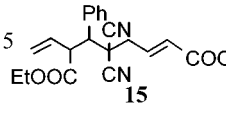
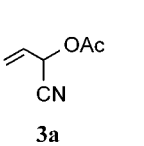
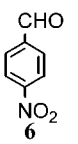
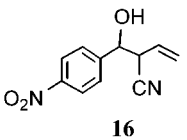
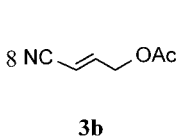
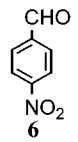
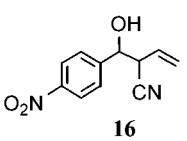
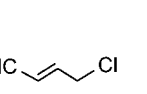
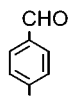
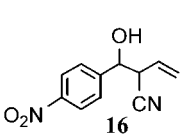
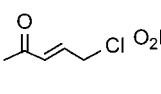
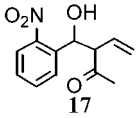
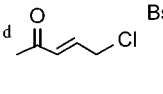
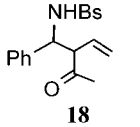


in THF (3 mL). Thereafter, the allylic substrate **1**−**5** (0.36 mmol or in the bisallylation reaction 0.7 mmol) was added, and this mixture was stirred for 10 min at room temperature under Ar. After addition of hexamethylditin (0.36 mmol) the reaction mixture was stirred for the allotted temperatures and times listed in Table 1. The products **10**−**18** were isolated by column chromatography using a pentane−EtOAc eluent.

Most of the reactions could be accomplished under mild conditions typically at 40 °C. All reactions proceed with an excellent regioselectivity. Reaction of **5** with benzenesulfonamid (Bs) derivative **7** (entry 11) provided **18** and the corresponding allylic isomer in a ratio of 12:1, while formation of a single regioisomer (**10**−**17**) was observed for the rest of the reactions. Selective formation of the branched allylic isomer is in sharp contrast to the regioselectivity observed for palladium-catalyzed nucleophilic substitutions.[5] An interesting demonstration of the contrasting regioselectivities in the electrophilic and the nucleophilic attack is given by the bisallylation reaction of **8** (entries 3 and 6). Yamamoto and co-workers[3b,c] have shown that the bisallylation reaction proceeds through an initial *electrophilic* attack on one of the allyl moieties followed by a *nucleophilic* attack on the other. The high regioselectivity in both processes is demonstrated by formation of a single regioisomer (**12** and **15**), in which the electrophilic carbon of **8** is attached to the branched allylic terminus, while the nucleophilic one is attached to the unsubstituted allylic terminus.

The diastereoselectivity of the reactions was dependent on the actual substrates and on the reaction conditions. A high diastereoselectivity could be achieved using allylic substrates **1** and **2** with electrophile **7** (entries 2 and 5). The high diastereoselectivity is particularly interesting for formation of **14**, as this product is a useful precursor in synthesis of β-amino acids.[6a] It was found that the diastereoselectivity of the reaction is lowered when PPh_3 was used as ligand. In place of allyl chlorides, allyl acetates could also be used as substrates (entries 7 and 8). However, this reaction does not proceed in the absence of phosphines. This is probably due to the fact that the palladium-catalyzed acetate stannane exchange cannot be accomplished without phosphine

Table 1. Palladium-Catalyzed Allylic Substitution of **1**−**5**

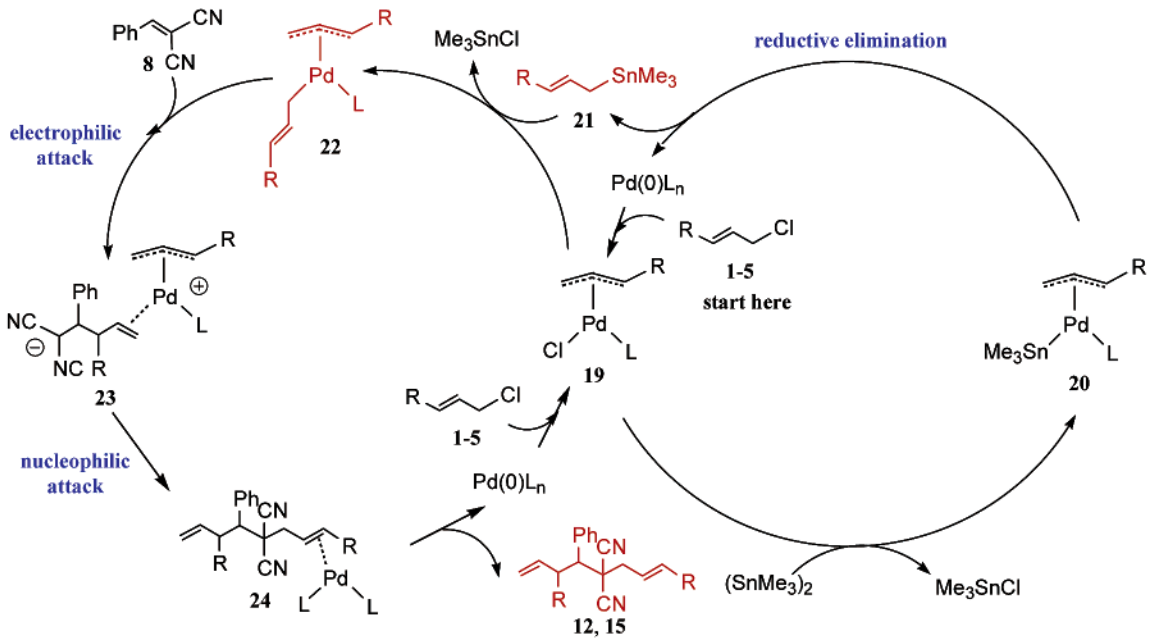
Entry	Allyl	Electrophile	Method[a]	Product	d.r.[b]	Yield[c]
1	 **1**	 **6**	A 40/14	 **10**	10:1	67
2	 **1**	 **7**	A 40/16	 **11**	>95:1	58
3	 **1**	 **8**	B 60/16	 **12**	2:1	60
4	 **2**	 **6**	A 20/16	 **13**	4:1	88
5	 **2**	 **7**	A 40/15	 **14**	>95:1	57
6	 **2**	 **8**	C 40/15	 **15**	2:1	70
7	 **3a**	 **6**	C 40/6	 **16**	1:1	61
8	 **3b**	 **6**	C 40/4	 **16**	1:1	58
9	 **4**	 **6**	A 40/6	 **16**	1:1	44
10	 **5**	 **9**	A 0/3	 **17**	2:1	57
11[d]	 **5**	 **7**	A 0/30	 **18**	2:1	54

[a] All reactions were conducted in THF in the presence of $(SnMe_3)_2$ using 5 mol % Pd catalyst. In Method A: $[\eta^3$-allyl)$PdCl]_2$. In Method B: the same catalyst and 5 mol % PPh_3. In Method C: $Pd(PPh_3)_4$. The allotted temperatures and times are given in °C/h. [b] Diastereomer ratio. [c] Isolated yield. [d] Compound **18** and its allylic isomer is formed in a ratio of 12:1. Bs = benzenesulfonyl.

(5) (a) Tsuji, J. *Palladium Reagents and Catalysis: Innovations in Organic Synthesis*; Wiley: Chichester, U.K., 1995; Chapter 4. (b) Godleski, S. A. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I.; Eds.; Pergamon Press: New York, 1991; Vol. 4, Chapter 3.3. (c) Szabó, K. J. *Chem. Soc. Rev.* **2001**, *30*, 136.

(6) (a) Ruano, J. L. G.; Fernández, I.; del Prado Catalina, M.; Hermoso, J. A.; Sanz-Aparicio, J.; Martínez-Ripoll, M. *J. Org. Chem.* **1998**, *63*, 7157. (b) Bumagin, N. A.; Kasatkin, A. N.; Beletskaya, I. P. *Izv. Akad. Nauk SSSR, Ser. Khim. (Engl. Transl.)* **1984**, 588. (c) Kisanga, P. B.; Verkade, J. G. *J. Org. Chem.* **2002**, *67*, 426. (d) Heathcock, C. H. *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 2, Chapter 1.5. (e) Jolly, P. W. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 3.

Scheme 2



cocatalyst.[6b] Usually, the yields are lower when allylic acetates are used as substrates; however, for cyano-substituted allylic substrates (**3a,b**) a higher yield was obtained than for the corresponding allyl chloride (**4**).

The reaction conditions are very mild, which allows a high level of functional group tolerance. The reactions proceed without addition of external base or Lewis acid catalyst. Furthermore, the central atom in the organometallic reagent, $(SnMe_3)_2$, is present in a high-oxidation state, and therefore undesired reduction processes can also be avoided. These mild reaction conditions allow the use of nitrobenzaldehydes (**6** and **9**) as electrophiles, which undergo side reactions or fail to react under basic or reductive conditions.[6c] The reaction products with electron-withdrawing substituents (**13**−**18**) are easily deprotonated, and therefore these compounds readily undergo base-catalyzed rearrangement and elimination reactions.[6c] Products formed by alkylation of **5** with aldehydes are sensitive to acidic conditions as well.

We have found that allyl chloride **5** smoothly reacts with **6**; however, the product (the *p*-nitro analogue of **17**) partially decomposes during silica gel chromatography. The chemoselectivity of the reaction is also high, as **5** could be alkylated without affecting the carbonyl functionality (entries 10 and 11). It is interesting to note that the regioselective alkylation of **5** at the branched allylic terminus is a particularly challenging task, since substitution of α,β-unsaturated ketons is usually expected at the γ-position.[6d]

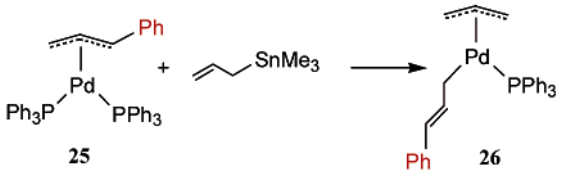
Since bisallylpalladium complexes easily undergo protonation,[6e] water has to be strictly excluded from the reaction mixture. This side reaction resulting in allylcyanide and but-3-enoic acid ethylester is a particularly important problem using substrates **2**−**4**. The protonation reaction can be largely avoided by using 4 Å molecular sieves added to the reaction mixture.

Mechanistic Considerations. Bumagin and Beletskaya[6b] have shown that hexamethylditin undergoes transmetalation with (η^3-allyl)palladium complexes, such as **19** (Scheme 2) affording complex **20**, which subsequently undergoes reductive elimination to give allylstannane **21**. Under catalytic conditions allyl chlorides (**1,2** and **4,5**) can be used as substrates in the presence of $[(\eta^3\text{-allyl})PdCl]_2$ as catalyst source. However, employment of allylic acetates as allyl precursors requires use of phosphine ligands.[6b] Under our reaction conditions the first step is supposed to be the palladium-catalyzed formation of the corresponding allylstannanes (**21**) from **1**−**5** and hexamethylditin. In fact, formation of the allylstannane product could be observed when the reaction of **1** with **6**−**8** was interrupted after 4 h.

Schwartz and Goliaszewski have shown[7a] that under catalytic conditions allyl chlorides and allylstannanes in the presence of palladium salts generate bisallylpalladium complexes. According to Yamamoto and co-workers[3a] the bisallylpalladium complexes formed in this way readily react with electrophiles such as aldehydes and imines. Furthermore, the same authors demonstrated that under catalytic conditions bisallylpalladium complexes may undergo a tandem bisallylation reaction.[3b] It is reasonable to assume that under our reaction conditions **21** formed in the first catalytic cycle undergoes transmetalation with monoallylpalladium complex **19** to generate bisallylpalladium complex **22**. In fact Mayr and Kuhn[7c] have shown that a diphosphine complex **25** analogue to **19** (R = Ph) readily reacts with allylstannane giving a bisallylpalladium species **26** (Scheme 3). A similar reaction is assumed to provide the key

(7) (a) Goliaszewski, A.; Schwartz, J. *Tetrahedron* **1985**, *41*, 5779. (b) Szabó, K. J. *Chem. Eur. J.* **2000**, *6*, 4413. (c) Kuhn, O.; Mayr, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 343. (d) Yamamoto, Y.; Hatsuya, S.; Yamada, J.-i. *J. Org. Chem.* **1990**, *55*, 3118.

Scheme 3



intermediate **22** (R = Ph) when **1** is employed as the allylic substrate (entries 1−3).

In a bisallylpalladium complex the allyl ligands can coordinate to the central atom with different hapticity. Recent mechanistic studies showed that the η^3,η^1-form of this complex is the active intermediate in the reactions with electrophilic reagents.[4,7b] In an η^3,η^1-bisallylpalladium complex the η^1-allyl moiety is nucleophilic, and therefore it is accessible for electrophilic reagents.[7b] The reaction with electrophiles **6**, **7**, and **9** affords the corresponding homoallyl alcohol and amine products. However, reagent **8** generates a malonitrile-type nucleophile along with a monoallylpalladium complex (**23**). Since the η^3-allyl moiety of a monoallylpalladium complex is electrophilic, complex **23** is converted to **24** and after decomplexation affords the bisallylated products **12** and **15**. A remarkable feature of this bisallylation process is that palladium catalyzes *three* different processes in the same catalytic cycle: an allylic substitution to provide **21**, an electrophilic attack to give **23**, and a nucleophilic attack leading to **24**.

The high reactivity of the transient allylstannanes to form **22** is very important for the overall reaction, since it is known that allylstannanes with allylic electron-withdrawing substituents are unstable and easily undergo polymerization reactions.[7d] An attractive feature of the above multiple catalytic approach is that it does not require the cumbersome isolation of these allylstannane derivatives.

The high regioselectivity is an important and synthetically useful feature of the presented reaction. Previous theoretical studies have shown that the electrophilic attack occurs at the C1 carbon in the η^1-moiety of the bisallylpalladium intermediate.[5c] We have carried out DFT calculations at the B3PW91/LANL2DZ(P) level of theory (Figure 1) to determine the stability of the four possible isomers of the η^1,η^3-bisallylpalladium intermediates (**27a**−**d**) that are expected

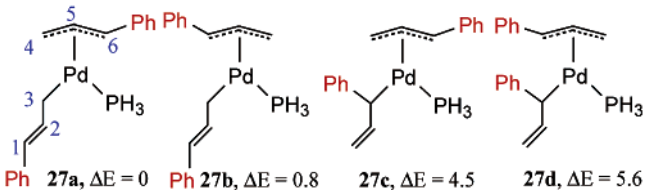


Figure 1. DFT energies [kcal mol^{-1}] of the isomeric bisallylpalladium complexes.

to form when cinnamyl chloride (**1**) is used as substrate (entries 1−3). The calculations clearly show that the bisallylpalladium intermediate is more stable when the phenyl group is attached to the C1 terminus of the η^1-allyl moiety (**27a,b**) than to the Pd-coordinated (C3) terminus (**27c,d**). These results are also in line with the observation of Mayr and Kuhn[7c] that the phenyl group prefers the C1 terminus in **26**. Since **27a** is the most stable form of the bisallylpalladium intermediate, an electrophilic attack occurring at the C1 terminus will afford the branched regioisomer.

In summary, we have shown that functionalized allylic substrates **1**−**5** can be alkylated with various electrophiles **6**−**9** by employment of hexamethylditin and catalytic amounts of palladium. The reaction proceeds with a remarkably high regioselectivity, and in certain cases (entries 1, 2, and 5) with a high stereoselectivity. In contrast to palladium-catalyzed nucleophilic substitution the present catalytic process provides the branched allylic product. This can be explained by the fact that the most stable bisallylpalladium intermediate is substituted at the C1 terminus of the η^1-allyl moiety, which is attacked by the electrophile.

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Supporting Information Available: Characterization and ^{13}C NMR spectra of products **10**−**18** and computational details for **27a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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